

**PROCESS FOR THE MANUFACTURE OF 3-AMINO-PYRROLIDINE****DERIVATIVES****Cross-Referenced To The Related Provisional Application**

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This Application claims the benefit of the European Application, Application No. 02016944.7, filed August 1, 2002.

**Background of the Invention**

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[0001] The present invention is concerned with a novel process for the manufacture of racemic and optically active 3-amino-pyrrolidine derivatives and with the use of this process for the production of cephalosporin derivatives.

20 [0002] 3-Amino-pyrrolidine derivatives, especially optically active 3-amino-pyrrolidine derivatives, are important intermediates for the production of agrochemicals and of pharmaceutically active substances such as, for example, of vinylpyrrolidinone-cephalosporin derivatives.

25 [0003] 3-Amino-pyrrolidine derivatives can be manufactured in a manner known per se, for example as described in EP-A-0 218 249 starting from 1,2,4-trisubstituted butane derivatives such as e.g. tribromobutane or trihydroxybutane. The racemic derivatives can then, if desired, be converted by

5 a racemate resolution into optically active 3-amino-pyrrolidine derivatives, as described in JP 09124595-A. A process for the manufacture of optically active 3-amino-pyrrolidine derivatives based on the conversion of 4-hydroxy-proline as described, for example, in J. Med. Chem. 1764(92), 35, gives optically active 3-aminopyrrolidine over 3 steps.

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[0004] The known methods for the manufacture of 3-aminopyrrolidine derivatives as described, for example, in UK Patent No. 1,392,194, EP-A-0 391 169 and US Patent No. 4,916,141, are time consuming and lead to expensive intermediates. The interest in other processes for the manufacture of 3-amino-  
15 pyrrolidine derivatives, especially of optically active 3-amino-pyrrolidine derivatives, is therefore extremely high. Thus, Tomori et al. (Heterocycles, 1997, 1, 213-225) have synthesized (S)-3-(t-butoxycarbonylamino)pyrrolidine from (S)-3-benzyloxycarbonylamino-1,4-dimethanesulfonyloxybutane by cyclization with excess allylamine and deallylation of the resulting (S)-1-allyl-3-  
20 (benzyloxycarbonylamino)pyrrolidine with palladium on charcoal. However, on a technical scale allylamine is unpractical, being a poisonous, inflammable and explosive liquid; also, palladium is an expensive catalyst.

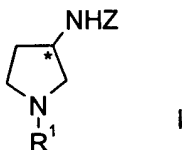
[0005] As can be seen, there is a need for a practical, safe, technical scale  
25 synthetic method for the synthesis of 3-aminopyrrolidine derivatives. Such a synthetic method should be cost effective and able to be performed safely on a large scale.

### Summary of the Invention

[0006] It was now found that 3-amino-pyrrolidine derivatives, especially optically active 3-amino-pyrrolidine derivatives, can be safely manufactured in high yield on a technical scale by replacing allylamine with hydroxylamine or its acid addition salt, particularly the hydrochloride, which is cheap and much easier to handle, having none of the disadvantages. Further, being a solid, hydroxylamine hydrochloride is easily soluble in polar organic solvents such as tetrahydrofuran, ethanol, triethylamine or mixtures thereof. The hydroxy group of the resulting N-hydroxy-3-protected-aminopyrrolidine is then removed by catalytic reduction with Raney nickel, which is a cheap catalyst.

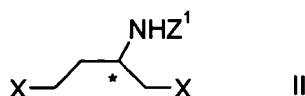
### Detailed Description of the Invention

[0007] In accordance with these findings, the invention is concerned with a process for the manufacture of 3-amino-pyrrolidine derivatives of the formula



wherein  
R¹ signifies hydrogen or an amino protecting group;  
Z signifies hydrogen or an amino protecting group;  
and  
\* represents a center of chirality,  
which process comprises converting a compound of the formula

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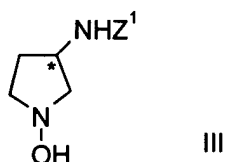
wherein

X signifies a protected hydroxy group;

Z¹ signifies an amino protecting group; and

\* has the above meaning,

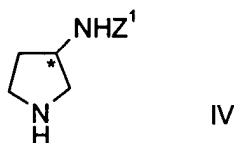
10 in the presence of hydroxylamine or an acid addition salt thereof into the N-hydroxy-pyrrolidine derivative of the general formula



wherein Z¹ and \* have the above meanings,

the N-hydroxy group of which is subsequently reduced to the secondary amine of

15 the general formula

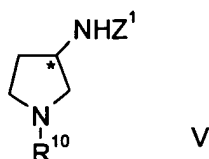


wherein Z¹ and \* have the above meanings,

by hydrogenation with Raney nickel; and, if desired, protecting the secondary N¹

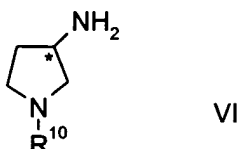
amino group by reaction with a compound of the formula R¹⁰X¹, in which R¹⁰ is an

20 amino protecting group and X¹ is halogen or a leaving group, to yield a compound of the general formula



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in which R<sup>10</sup>, Z<sup>1</sup> and \* have the above meanings,  
and, if desired, deprotecting the secondary 3-amino group by catalytic  
hydrogenation to yield a compound of the general formula



10 in which R<sup>10</sup> and \* have the above meanings.

[0008] Under the above definitions the term "protected hydroxy group" in the scope  
of the present invention encompasses ester groups, for example, sulfonates  
such as mesylate, tosylate, p-bromobenzenesulphonate or p-  
15 nitrobenzenesulphonate. These are especially groups which are cleaved off  
selectively under the reaction conditions for the ring closure such that the  
amino protecting group Z in the 2-position is not liberated. Mesylate and  
tosylate (mesyloxy and tosyloxy) are especially preferred protected hydroxy  
groups X.

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[0009] The term "amino protecting group" in the scope of the present invention  
encompasses lower alkyl, benzyl, lower alkenyl, lower alkoxy carbonyl, lower  
alkenyloxy carbonyl, benzyloxy carbonyl and the like. t-Butoxy carbonyl,  
allyloxy carbonyl and benzyloxy carbonyl, particularly the latter, are especially  
25 preferred.

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[0010] The term "leaving group" embraces halogen atoms, such as chlorine or bromine, and lower alkylsulfonyloxy or lower alkylphenylsulfonyloxy groups such as mesyloxy or tosyloxy, also anhydride residues of carbonic acid such as t-butoxycarbonyloxy.

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[0011] The term "lower alkyl" in the scope of the present invention encompasses straight-chain and branched, optionally chiral hydrocarbon groups with 1 to 8 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, i-propyl, i-butyl, tert-butyl, 2-methylbutyl and the like. "Lower alkoxy" has analogous significance .

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[0012] The term "lower alkenyl" encompasses olefinic, straight chain and branched groups with 2 to 8 carbon atoms such as vinyl, allyl, 3-butenyl, 1,3-butadienyl.

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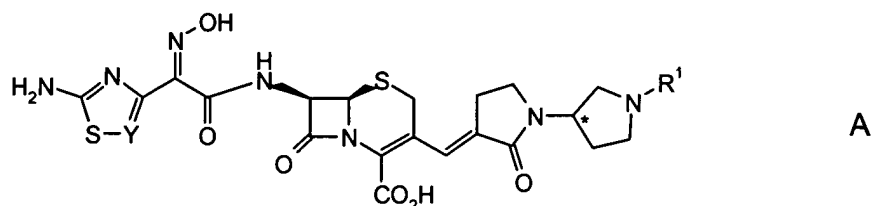
[0013] The terms "lower allyl", "lower alkoxy" and "lower alkenyl" keep their meanings in combinations e.g. with "carbonyl", e.g. t-butoxycarbonyl, allyloxycarbonyl.

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[0014] In an especially preferred aspect of the process of the present invention optically active R-form of 2-(benzyloxycarbonylamino)-1,4-dimethanesulfonyloxybutane is cyclized with hydroxylamine hydrochloride at about 0°C to the boiling point of the reaction mixture in a polar solvent such as tetrahydrofuran, ethanol, triethylamine or dimethylsulfoxide or a mixture thereof, quite preferably in triethylamine. Subsequently, the hydroxy group of the

5 resulting N-hydroxy-3-protected pyrrolidine of formula III is reductively removed  
by hydrogenation with Raney nickel at room temperature in a hydrogen  
atmosphere. The resulting secondary amine of formula IV can subsequently be  
N-protected, preferably by t-butoxycarbonyl, by reaction with di-t-butyl-  
dicarbonate, preferably at room temperature. The benzyloxycarbonyl protecting  
10 group of the resulting di-protected product of formula V is expediently removed  
catalytically with hydrogen and palladium on charcoal, preferably at room  
temperature.

[0015] The resulting primary amine of formula VI is especially suitable for  
15 manufacturing vinylpyrrolidinone-cephalosporin derivatives of the general  
formula



wherein

Y signifies CH or nitrogen;

20 R<sup>1</sup> denotes hydrogen or an amino protecting group; and

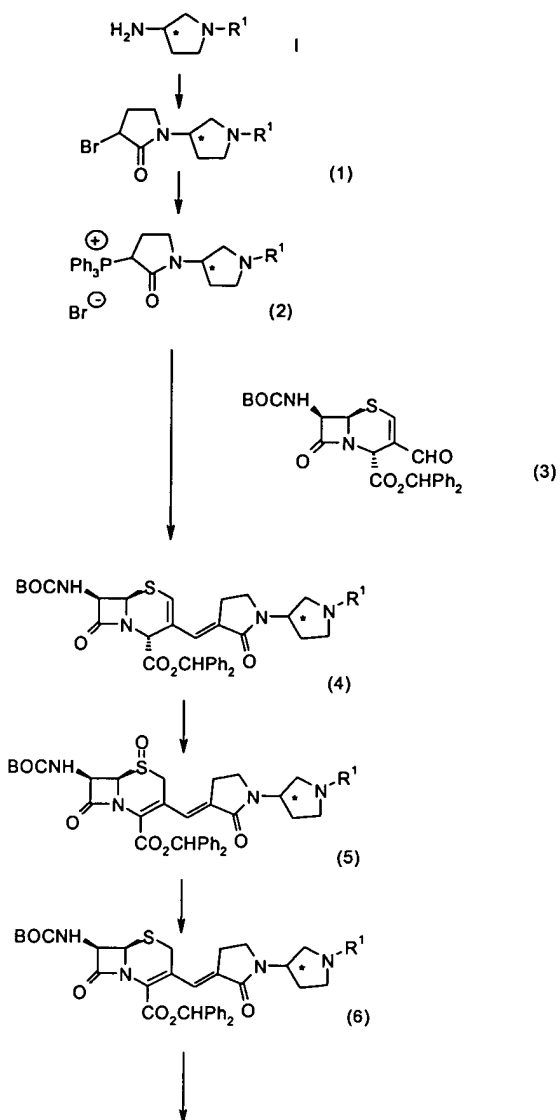
\* denotes a center of chirality.

[0016] Compounds of formula A are cephalosporin derivatives having a high  
antibacterial activity, especially against methicillin-resistant strains of  
25 *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*.

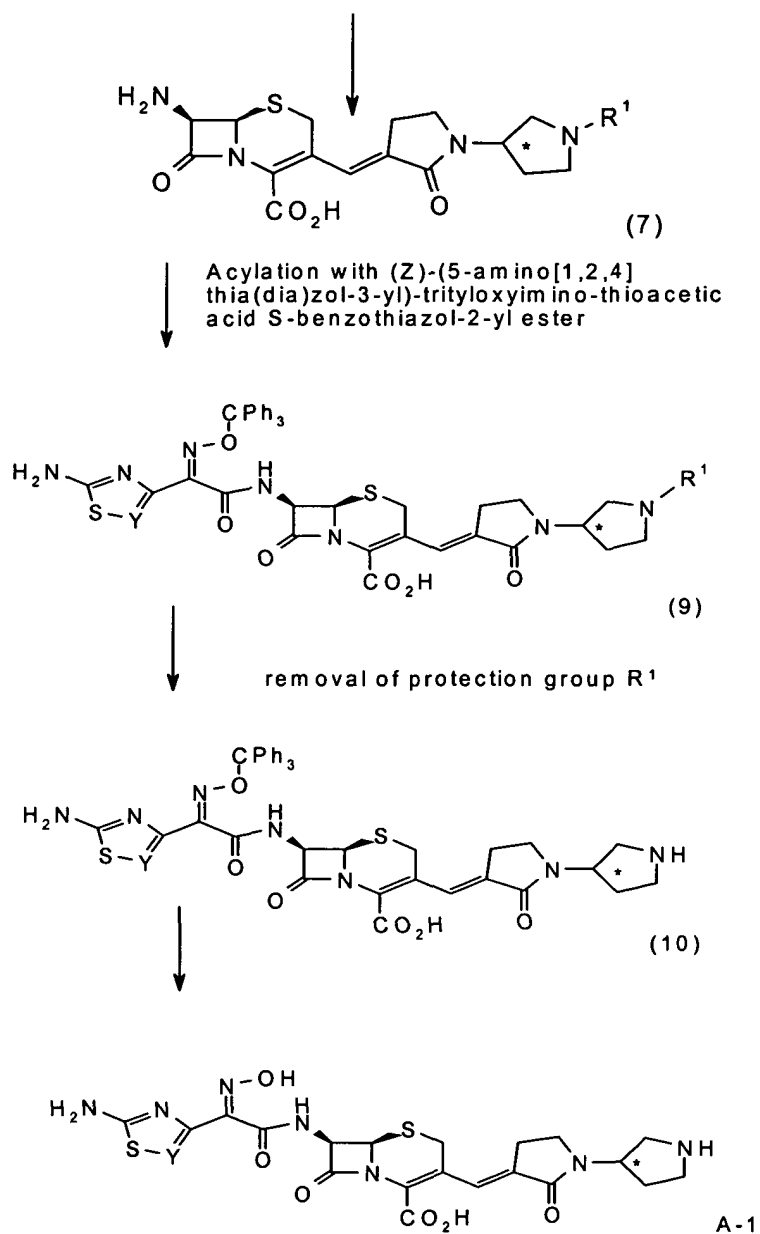
- 5 [0017] Compounds of the general formula A can be produced as per EP-A-849 269 in accordance with Scheme I:



## Scheme 1



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[0018] In Scheme 1 Y, R<sup>1</sup> and \* have the above significance; Ph is phenyl, BOC is t-butoxycarbonyl and CHPh<sub>2</sub> is benzhydryl.

[0019] For obtaining the compounds of the general formula A the 3-amino-pyrrolidine derivative of formula I are manufactured in accordance with the invention according to the method described above, thereafter reacted in accordance with Scheme 1 with 2-bromo-4-chlorobutanoyl chloride, and the N-substituted 3-bromo-2-pyrrolidone (1) so obtained is converted into the Wittig salt (2) which is reacted with the diprotected 3-ene cephalosporin (3). The resulting condensation product (4) is oxidized to the 5-sulfoxide (5) which is reductively isomerized with  $\text{PBr}_3$  to the 2-ene cephalosporin (6), the latter is N-deprotected and acylated with the activated acyl derivative (8) to yield (9) which is deprotected in two steps to yield (10) and finally the end product of formula A.

[0020] The following Examples serve to illustrate the invention.

#### Example 1

##### (R)-3-(Benzyloxycarbonylamino)-N-hydroxy-pyrrolidine.

[0021] (R)-2-(Benzyloxycarbonylamino)-1,4-dimethanesulfonyloxybutane (2.0 g; 5.06 mmol) was dissolved in a  $\text{Et}_3\text{N}/\text{DMSO}$  mixture (1:1, 20 ml). Hydroxylamine hydrochloride (1.4 g; 20.2 mmol) was added and the mixture was heated at  $60^\circ\text{C}$  over night. The mixture was poured in aqueous  $\text{HCl}$  (the pH was adjusted to  $\text{pH}=6$  with  $\text{NaHCO}_3$ ) and extracted twice with  $\text{AcOEt}$ . The organic phase was washed with water and dried over  $\text{Na}_2\text{SO}_4$ . The solids were filtered off and the

5 solvent was removed. A light yellow oil (1.4 g, purity 73%) was obtained (yield: 85%). The crude title compound was used as is.

### Example 2

#### 10 (R)-3-(Benzyloxycarbonylamino)-N-(t-butoxycarbonyl)-pyrrolidine.

[0022] The crude (R)-3-(benzyloxycarbonylamino)-N-hydroxy-pyrrolidine obtained above (1.4 g) was dissolved in ethanol (10 ml). Raney nickel (about 2 g) was added to this mixture. The reaction was degassed under reduced pressure and  
15 hydrogen supply (three times) and subsequently put under hydrogen atmosphere (1 bar). The reaction was over after 6 hours, yielding crude (R)-3-(benzyloxycarbonylamino)-pyrrolidine which was further processed in situ, in that di-tert-butyl dicarbonate (1.0 g, 4.58 mmol) was added; the mixture was stirred for one hour. The solvent was removed and the residue taken up in an  
20 n-hexane/AcOEt mixture (1:1, 20 ml) and filtered through a silicagel pad. The silica was washed with n-hexane/AcOEt mixture (1:1; 250 ml). The organic phases were evaporated. The compound was obtained as a colorless oil (1.125 g; yield 81%) in good purity, i.e. at least 90 - 95 %, rendering the compound sufficiently pure for further reaction, e.g. in Example 3.

25 NMR: (CDCl<sub>3</sub>; 300 MHz): 7.34 (m;5H); 5.1 (s(broad); 2H; 4.83 (m(broad); 1H); 4.22 (m(broad); 1H); 3.60 (dd; 1H); 3.41 (m(broad); 2H); 3.18 (m(broad); 1H); 2.12 (m; 1H); 1.82 (m(broad); 1H); 1.45 (s; 9H).  
MS: (M+H<sup>+</sup>): 321.3 (M+NH<sub>4</sub><sup>+</sup>): 338.2

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5 [0023] Example 2 may also be carried out under pressure in a pressure reactor at  
a pressure range of 1 to 50 kg, more preferred 1 to 20 kg, most preferred at a  
pressure of 3.8 kg. Further the reaction may be carried out at a temperature  
between 20 °C and 100 °C, more preferred 40°C to 60 °C, most preferred the  
reaction may be carried out at a temperature of 55 °C.

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### Example 3

#### (R)-3-Amino-N-(t-butoxycarbonyl)-pyrrolidine.

15 [0024] (R)-3-(Benzyloxycarbonylamino)-N-(t-butoxycarbonyl)-pyrrolidine (300 mg)  
was dissolved in ethanol (5 ml). Palladium on charcoal 10% (20 mg) was  
added. The reaction was degassed three times and put under hydrogen  
atmosphere (1 bar). The reaction was over after 2 hours. The solvent was  
removed, the residue was taken up in ethyl acetate (5 ml) and filtered through a  
20 silica gel pad. The silica was washed with ethyl acetate (50 ml). The organic  
phases were evaporated. The desired (R)-3-Amino-N-(t-butoxycarbonyl)-  
pyrrolidine was obtained as a colorless oil in a quantitative yield (175 mg).

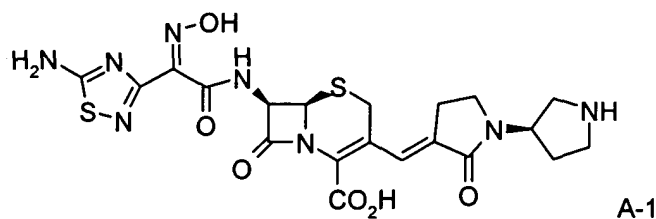
NMR: (CDCl<sub>3</sub>; 300 MHz): 3.6-3.3 (m(broad); 3H); 3.05 (m(broad); 1H); 2.29  
25 (s(broad); 2H); 2.05 (m; 1H); 1.66 (m(broad); 1H); 1.46 (s; 9H).

MS: (M+H<sup>+</sup>): 187.3

[0025] Example 3 may also be carried out under pressure in a pressure reactor at  
a pressure range of 1 to 50 kg, more preferred 5 to 40 kg, most preferred at a  
30 pressure of 20 kg. Further the reaction may be carried out in the presence of an

5 acid (after the addition of Pd/C), such as acetic acid, HCl or perchloric acid.  
Most preferred perchloric acid is used.

[0026] The (R)-3-amino-N-(t-butoxycarbonyl)-pyrrolidine can be utilized in Example  
2 of EP-A-0 849 269 instead of the N-allyloxycarbonyl derivative and  
10 subsequently in Examples 3-11 to yield (6R,7R)-7-[(Z)-2-(5-amino-  
[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetyl-amino]-8-oxo-3-[(E)-(R)-2-oxo-  
[1,3']bipyrrolidinyl-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-  
carboxylic acid of the formula



15 Example 4

[0027] A 200 l reactor was charged with 27 l of dimethylsulfoxide, 9.5 kg of (R)-2-  
(benzyloxycarbonylamino)-1,4-dimethanesulfonyloxybutane and 6.68 kg of  
hydroxylamine hydrochloride and the reaction mixture stirred at room  
20 temperature to suspend. 27 l of triethylamine were added slowly, whereupon  
the temperature rose to 45 - 50 °C. The reaction mass was maintained at 55 °C  
for four hours. The reaction was monitored by NMR or HPLC (high  
performance liquid chromatography). Subsequently the reaction mixture was  
cooled to room temperature.

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- 5 [0028] Separately a solution was prepared with 100 l of water at 0 °C containing  
14.2 l of concentrated aqueous hydrochloric acid. The above reaction mass  
was added to this solution and the pH value checked to 1.0 to 1.5. The  
aqueous layer was washed twice with each 10 l of 1:1 ethyl acetate and n-  
hexane and neutralized with 15 kg of sodium bicarbonate. The reaction mixture  
10 was stirred for 30 minutes and the pH checked to about 7.0 - 7.5. The aqueous  
layer was extracted three times with 15 l of ethyl acetate each time. The  
combined organic phases were washed twice with each 15 l of water followed  
by 10 l of brine (saturated aqueous sodium chloride solution).
- 15 [0029] The solvent was evaporated at reduced pressure, at the end of which the  
oily residue was stripped with 10 l of n-hexane. The n-hexane was evaporated  
off, n-hexane added again and the mixture stirred to precipitate the product.  
The crude (R)-3-(Benzyloxycarbonylamino)-N-hydroxy-pyrrolidine was filtered  
off and used directly in example 5. The white solid obtained changed to yellow  
20 upon storage.

[0030] Yield 4.6 - 5.0 kg (80 - 85 %) having a purity of more than 95 %.

Example 5

[0031] A 50 l autoclave was charged with 22.5 l of ethanol, 4.5 kg of (R)-3-(benzyloxycarbonylamino)-N-hydroxy-pyrrolidine and 1.35 kg of Raney nickel. The autoclave was put under hydrogen atmosphere (50 psi = 3.5 bar) and stirred for four hours. The reaction was monitored by HPLC and TLC.

[0032] After reaction the catalyst was filtered off and the solvent removed by evaporation at reduced pressure. The residue, crude (R)-3-(benzyloxycarbonylamino)-pyrrolidine, was dissolved in 20 l of ethanol followed by 4.15 kg of di-tert-butyl dicarbonate. The reaction mixture was stirred at room temperature for two hours, the reaction being monitored by HPLC and TLC. The solvent was evaporated off at reduced pressure, the reaction mixture being stripped twice by the addition of 2 l of toluene each time.

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[0033] 5.7 kg of crude (R)-3-(benzyloxycarbonylamino)-N-(t-butoxycarbonyl)-pyrrolidine was obtained as a yellowish oily residue, which was purified by dissolution, in a 20 l reactor, in 11.4 l of methylene chloride followed by 2.85 kg of silica gel and 57 g of charcoal. The reaction mixture was stirred for two hours at room temperature. The solids were filtered off and washed thoroughly with 10 l of methylene chloride. The combined organic layers were evaporated at reduced pressure, yielding 5.1 kg of (R)-3-(benzyloxycarbonylamino)-N-(t-butoxycarbonyl)-pyrrolidine as a colorless oil.

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Example 6

[0034] An autoclave was charged with 51 l of ethanol, 5.1 kg of (R)-3-(benzyloxycarbonylamino)-N-(t-butoxycarbonyl)-pyrrolidine, 0.51 g of 5 % palladium-on-carbon and 0.5 l of perchloric acid. The autoclave was put under hydrogen atmosphere (100 psi = 7 bar) for one hour, the reaction being monitored by NMR. After completion of the reaction the catalyst was filtered off and the solvent removed under reduced pressure.

[0035] The oily residue was dissolved in 10 l of ethyl acetate and the organic layer washed with 10 l of water, followed by 10 l 10 % aqueous sodium carbonate solution. The organic phase was dried over sodium sulfate and the solvent removed by evaporation under reduced pressure. 2.5 kg of (R)-3-Amino-N-(t-butoxycarbonyl)-pyrrolidine was obtained as a colorless oil.

[0036] The NMR spectrum is identical with that reported under Example 3.

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[0037] All references discussed throughout the above specification are herein incorporated in their entirety by reference for the subject matter they contain.

[0038] It should be understood, of course, that the foregoing relates to preferred embodiments of the invention and that modifications may be made without departing from the spirit and scope of the invention as set forth in the following claims.

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